REMARKS/ARGUMENTS

With this amendment, claims 1-7, 16-22 and 45 are pending. Claims 3-6, 17, and 19-22 are withdrawn. Claims 8-15 and 23-44 are cancelled without prejudice. New claim 45 is added. For convenience, the Examiner's rejections are addressed in the order presented in an March 21, 2007, Office Action

I. Status of the claims

Claim 1 and dependent claims are amended to recite identifying a compound that modulates cell proliferation. Support for these amendments is found throughout the specification, for example at page 36, line 10 through page 37, line 9; page 47, lines 5-15; page 50, lines 1-7; and Figures 67 and 68. Claim 1 is also amended to recite use of an A549 cell or an H1299 cell. Support for this amendment is found throughout the specification, for example, at Figures 67 and 68. New claim 45 recites that a FEN1 D181A mutant inhibits cell growth when expressed in an A549 cell. Support for this amendment is found throughout the specification, for example, at Figures 66 and 67. These amendments add no new matter.

II. Rejections under 35 U.S.C. §102(b)

Claims 1, 7-9, 11, 12, 15, 16, and 18 are rejected as allegedly anticipated by Harrington *et al.* (US Patent No. 5,874,283). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited references must contain every element of the claims at issue. The cited reference does not.

Claim 1 is now amended to recite that an A549 cell or an H1299 cell comprising a heterologous FEN1 polypeptide is contacted with the test compound and then cell proliferation effects are assayed. Harrington *et al.* does not disclose use of either an A549 cell or an H1299

cell for cell proliferation assays. The Office Action indicates that, at a minimum, no prior art was found on cell cycle arrest assays of A549 cells that express a heterologous FEN1 polypeptide. *See, e.g.*, Office Action at page 3. Therefore, Harrington *et al.* does not disclose all the elements of the invention and cannot anticipate the claims.

In view of the above amendments and remark, withdrawal of the rejection for alleged anticipation is respectfully requested.

III. Rejections under 35 U.S.C. §103(a)

Claim 2 is rejected as allegedly obvious over Harrington *et al.* in view of Shibata *et al. J. Biol. Chem.* 277:746-754 (2002). According to the Office Action Shibata *et al.* teach expression of dominant negative FEN1 mutants alters the level of cell cycle checkpoint proteins and those of skill would have been motivated to practice the cell cycle assays allegedly disclosed in Harrington *et al.* using Shibata *et al.* mutants with altered biological activity. To the extent the rejection applies to the amended claims, Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be come suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the limitations of the claims. MPEP§2143. See also *In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level or skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, teaching, or motivation to combine must be "clear and particular." *In re Dembiczak,* 50 USPQ2d 1614, 1617 (1999). With respect to the desirability to combine, the mere fact that references *can* be combined or modified does not render the resultant combination obvious. *In re Mills,* 16 USPQ2d 1430 (1990). Additionally, the fact that individual components of a claimed invention are conventionally employed in the art for the same purpose does not present a case of

prima facie obviousness. *In re Geiger*, 2 USPQ2d 1276 (1987). The Office Action does not provide a *prima facie* case of obviousness.

The Office Action appears to suggest that the combination of Harrington *et al.* and Shibata *et al.* would lead those of skill to assay any cell type expressing a dominant negative FEN1 protein for effects on the cell cycle. However, Harrington *et al.* disclose only the FEN1 polypeptide and identification of compounds that modulate the activity of the FEN1 polypeptide by reducing a cell's ability to repair DNA damage. Shibata *et al.* disclose only that expression of the FEN1 mutant polypeptide in a bladder carcinoma cell slows DNA repair caused by exposure to MMS. Similarly, Harrington *et al.* discuss only the effect of FEN1 modulators on the DNA repair pathway without disclosure of, *e.g.*, use of NIH3T3 cells, HeLa cells or CHO cells.

The amended claims are directed to use of an A549 cell or H1299 cell that expresses a heterologous FEN1 polypeptide to determine the effect of a compound on cell proliferation. The claims are based on experimental results that demonstrate that expression of a dominant negative FEN 1 polypeptide (*e.g.*, FEN1 D181A) in A549 cells and H1299 cells inhibited proliferation of the cells. The results are disclosed in Figures 66-68. In contrast, Shibata *et al.* assayed proliferation of a human bladder carcinoma cell line that expressed the same FEN1 D181A mutant and found that proliferation was not affected as compared to the cells that expressed the wild-type FEN1 protein. *See, e.g.*, Shibata *et al.* Figure 2C and page 748, right column. Based on the disclosures of Harrington *et al.* and Shibata *et al.* those of skill would predict that inhibition of FEN1 or expression of a FEN1 dominant negative mutant would have no effect on cell proliferation. Given that Shibata *et al.* disclose that expression of the FEN1 dominant negative mutant has no effect on cell proliferation, those of skill would have no reason to expect success in assaying for a compound that modulates cell proliferation by modulating FEN1 activity or to expect a different proliferation result when comparing expression of the wild-type FEN1 polypeptide to expression of the dominant negative FEN1 polypeptide.

Moreover, neither Harrington *et al.* nor Shibata *et al* disclose use of A549 or H1299 cells in an assay for modulation of FEN1 activity. Thus, even when combined, the cited references do not disclose all the elements of the claimed invention.

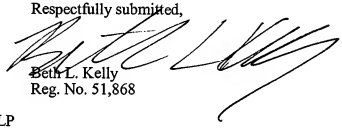
In view of the above-amendments and remarks, withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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